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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
JOHANNSEN, DIANA B

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/950,016	WARRINGTON ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *3-6,15-17 and 26-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-14 and 18-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0402* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Amendment filed January 7, 2002, and the paper and computer readable forms of the Sequence Listing filed February 28, 2002, have been entered.

Election/Restriction

2. Applicant's election without traverse of Group I, claims 1-2, 7-14, and 18-25, in the Response filed April 25, 2003, is acknowledged.

3. Claims 3-6, 15-17, and 26-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the Response of April 25, 2003.

Specification

4. The use of the trademarks GENECHIP®, SUPERSCRIPT™, RIBOGREEN®, GENBANK™, TAQMAN®, SYBR®, MACVECTOR®, and MATLAB™ has been noted in this application. The trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2, 7-14, and 18-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of diagnosing oral cancer in a human subject that comprise detecting an altered level of expression of a gene or genes whose differential expression is/are known to be associated with oral cancer, and for methods of monitoring the expression of such genes, does not reasonably provide enablement for methods of diagnosing oral cancer or of monitoring expression levels in which any gene "associated with oral cancer" is detected, for methods of diagnosing oral cancer in non-human subjects, or for methods of "monitoring the progression" of cancer in a subject in which marker expression levels at different time points are detected in order to "monitor the progression of oral cancer." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Claims 1-2 are drawn to methods of monitoring gene expression in which arrays of probes are used to determine the relative hybridization/relative binding of array probes to nucleic acids derived from cells from malignant oral tissue. Claims 7-14 and 18-21 are drawn to methods of diagnosing oral cancer in which differences in levels of expression of markers "associated with oral cancer" in a subject sample as compared to a control sample are indicative of cancer. Claims 22-25 are drawn to methods of monitoring the progression of oral cancer in which the levels of markers "associated with oral cancer" are detecting at multiple time points and compared "in order to monitor the progression of oral cancer."

It is unpredictable as to whether one of skill in the art could use applicants' invention in a manner reasonably commensurate with the instant claims. The specification discloses particular groups of genes that were found to be upregulated and downregulated in oral cancer tissue samples taken from human subjects (see pages 19-23, Figure 2), and discloses that the results obtained by microarray analysis were confirmed by real-time PCR (see pages 23-24). Given the data provided in the specification, upregulation of one or more of the genes found by Applicants to be upregulated in oral cancers, and/or down regulation of one or more of the genes found by Applicants to be downregulated in oral cancers, are clearly among factors that one of skill in the art would reasonably consider in diagnosing oral cancer in a human subject. However, the instant specification is silent with respect to any genes whose expression is either upregulated or downregulated in oral cancer in non-human subjects, and further, provides no evidence that various levels of expression, e.g., correlate with tumor

stage in any type of subject, as would be necessary in order for one to monitor tumor progression by detecting marker expression levels at various time points. Further, the instant claims are not limited to the particular genes identified by Applicants as being up- or downregulated in oral cancers, but rather encompass the detection of any genes "associated with oral cancer" in any way, or (in the case of, e.g., claim 2), to monitoring the expression of any gene or genes. While one of skill in the art could clearly diagnose oral cancer in a human subject by detecting upregulation of genes known to be upregulated in such cancers, or by detecting downregulation of genes known to be downregulated, one of skill in the art could not practice such methods by detecting, e.g., downregulation of a gene that is upregulated in oral cancers, or by detecting alterations in expression levels of genes that are "associated with oral cancer" in other ways (e.g., genes that are mutated in oral cancers but whose expression levels are not altered). Lacking guidance from the specification, one of skill in the art may look to the teachings of the art for additional guidance and enablement of a claimed invention. In the instant case, the prior art as exemplified by Chang et al (Oncogene 16:1921-1930 [4/1998]) does teach several genes whose expression levels are altered in oral cancers in humans (see entire reference, particularly page 1924), and one of skill in the art could clearly detect altered levels of such markers as indicators of oral cancer. However, the prior art does not provide further guidance with respect to detection of oral cancers in non-human subjects, or with respect to diagnosis of cancer by detecting altered expression of "genes associated with oral cancer" that are not known to exhibit altered expression in cancer. Further, the prior art as exemplified by Ibrahim et al (Oral

Oncology 35:302-313 [5/1999]) discloses that no statistically significant correlation was found between tumor grade and expression levels of a group of oral cancer markers examined in oral cancer tissues taken from patients with different grades of tumors (see entire reference, particularly pages 308-309). As neither the specification nor the prior art provide evidence that one could monitor progression of oral cancer in a subject by detecting expression levels of any type of oral cancer associated gene at various time points, it is unpredictable as to whether any quantity of experimentation would allow a skilled artisan to practice such methods. Accordingly, while the teachings of the specification and of the art would enable one of skill in the art to practice methods of diagnosing oral cancer in a human subject that comprise detecting an altered level of expression of a gene or genes whose differential expression is/are known to be associated with oral cancer, and for methods of monitoring the expression of such genes, it would require undue experimentation to use Applicants' invention in a manner reasonably commensurate with the instant claims.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-2, 7-14, 18-22, and 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is unclear as to how the recited steps of "contacting an array of probes with a population of nucleic acids" and "determining relative hybridization of the probes to the population" result in "monitoring expression of

one or more genes associated with oral cancer in one or more cells," as recited in the claim preamble. It is noted that the method steps recited in the claim never refer to "one or more genes associated with oral cancer;" accordingly, the manner in which the recited method steps achieve such monitoring of "one or more genes" is unclear. Clarification is required.

Claim 2 is indefinite over the recitation "the probes" in line 6 of the claim. It is noted that the claim previously refers to a "first array of probes" and a "second array of probes." It is unclear as to whether the recitation "the probes" refers to the first array, the second array, or to both arrays (i.e., such that the claim is intended to be drawn to a method in which identical arrays of probes are employed as "first" and "second" arrays). Clarification is required.

Claims 7-14 and 18-21 are indefinite over the recitation of the limitation "the marker" in claim 7 because there is insufficient antecedent basis for this limitation in the claims. While claim 7 previously refers to "at least one marker" and a "group of markers," it does not previously recite a single "marker."

Claims 11-14 are indefinite over the recitation of the limitation "the sample" in claim 11. Claim 7, from which claim 11 depends, recites multiple samples (a "sample from a subject" and a "control sample"), and it is unclear as to which of these samples constitutes "the sample" referred to in claim 11.

Claims 11-14 are indefinite over the recitation "the probes" in lines 7-8 of claim 11. It is noted that the claim previously refers to a "first array of probes" and a "second

array of probes." It is unclear as to whether the recitation "the probes" in each instance refers to the first array, the second array, to both arrays, etc. Clarification is required.

Claims 12-13 are indefinite over the recitation of the limitation "the nucleic acid" in each of the claims because there is insufficient antecedent basis for the limitation in the claims.

Claim 14 is indefinite over the recitation of the limitation "the array of probes." Because multiple probe arrays are recited in claim 11 (from which claim 14 depends), it is unclear as to which array constitutes "the array of probes."

Claims 18-21 are indefinite over the recitation of the limitation "the marker" in claim 18, because there is insufficient antecedent basis for this limitation in the claims. While claim 7 previously refers to "at least one marker" and a "group of markers," it does not previously recite a single "marker."

Claims 18-21 are indefinite over the recitation of the limitation "the sample" in claim 18. Claim 7, from which claim 18 depends, recites multiple samples (a "sample from a subject" and a "control sample"), and it is unclear as to which of these samples constitutes "the sample" referred to in claim 18.

Claims 23-25 are indefinite over the recitation of the limitation "the sample" in claim 23. Claim 22, from which claim 23 depends, recites multiple samples (a "sample obtained from the subject at a first point in time" and a "sample obtained from the subject at a subsequent point in time"), and it is unclear as to which of these samples constitutes "the sample" referred to in claim 23.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Chang et al (Oncogene 16(15):1921-1930 [4/1998]).

Chang et al disclose methods in which the expression of genes associated with oral cancer are monitored by hybridization of nucleic acids from various types of cell samples with arrays of cDNAs expressed preferentially in normal cells and cDNAs expressed preferentially in HPV-immortalized cells (see entire reference, particularly pages 1923-1924, 1929). The samples monitored by Chang et al include cells "derived from normal tissue" (specifically, both NHOK cells and HPV-immortalized oral epithelial cells are "derived from normal tissue") and cells "derived from malignant oral tissue" (specifically, the oral cancer cells monitored by Chang et al)(see pages 1922-1924). Chang et al further determine the relative binding of arrayed probes to the different population of nucleic acids, and identify probes that are differentially expressed (see, e.g., page 1924). Accordingly, Chang et al clearly anticipate claims 1-2.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 7-9, 11-14, and 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levine et al (U.S. Patent No. 6,171,798 [01/09/2001; effective filing date 3/27/1998]) in view of Chang et al (Oncogene 16(15):1921-1930 [4/1998]).

Levine et al disclose methods of diagnosing cancer in a subject in which the level of expression of one or more cancer markers in a subject is compared to marker levels in a control, wherein a significant difference in levels is indicative of cancer (see entire reference, particularly, e.g., col 1, line 49-col 2, line 17; claims 1-33). While Levine et al disclose the use of their method in detecting "cancer" in general, and teach the use of tissue samples in their methods (see, e.g., col 1, line 49-col 2, line 17; col 4, lines 53-65), Levine et al do not specifically teach detection of oral cancer, or teach the use in their method of cells obtained from oral tissue. Chang et al teach a group of genes that are differentially expressed in oral cancer cells as compared to normal controls (see entire reference, particularly page 1924). In view of the teachings of Chang et al, it

would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Levine et al so as to have employed the method in diagnosing oral cancers by detecting the levels of markers known to be differentially expressed in oral cancer in samples, including oral tissue samples, from a subject suspected of having oral cancer, and comparing those levels to levels in normal controls. An ordinary artisan would have been motivated to have made such a modification for the advantage of more rapidly diagnosing the presence of oral cancer. It is further noted that as Chang et al disclose the identity of a group of genes whose expression levels differ from levels in normal cells in at least some types of oral cancer cells, the levels of said genes are one factor, among others, that an ordinary artisan would reasonably consider in diagnosing oral cancer.

Regarding claims 11-14, it is noted that Levine et al disclose the use of arrays of probes, which arrays are hybridized to both test and control samples in order to quantify and determine relative hybridization (see, e.g., col 4, lines 26-52; claims 1-33). Regarding claims 12-13 and 18-20, Levine et al disclose the detection of both cDNA and RNA targets (see, e.g., col 5, lines 25-37). Regarding claims 14 and 21, Chang et al disclose amplification of nucleic acids prior to array hybridization (see, e.g., page 1929).

14. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Levine et al in view of Chang et al, as applied to claims 7-9, 11-14, and 18-21, above, and further in view of Ts'o et al (U.S. Patent No. 5,962,237 [10/05/1999; filed 04/02/1997]).

The teachings of Levine et al and Chang et al are set forth in the preceding paragraph. Levine et al and Chang et al do not teach detection of oral cancer markers in blood cells, as required by claim 10. Ts'o et al disclose that cancer cells present in the blood are indicative of cancer metastasis, and disclose methods for enriching such cells so as to facilitate detection of cancer metastasis, stating that enrichment of such cells is "of great diagnostic benefit" (see entire reference, particularly col 1, lines 22-34). In view of the teachings of Ts'o et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Levine et al and Chang et al so as to have employed therein cells "obtained from blood cells" of the subject, and to have compared marker expression levels in such cells with levels in normal controls. An ordinary artisan would have been motivated to have made such a modification for the advantage of rapidly detecting metastasis of oral cancer, as suggested by Ts'o et al.

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B Johannsen

Diana B. Johannsen
July 25, 2003